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THE NEURONE THEORY IN THE LIGHT OF RECENT DISCOVERIES.[1]

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THE nervous system differs from all other systems of organs in that its cellular elements show the highest degree of differentiation. Thus, in the digestive system, the destruction of a few liver cells means only a minute diminution in the amount of bile secreted, a loss that can be entirely replaced through the slightly increased activity of the remaining cells; and in the muscular system the removal of a few muscle fibres from a given muscle may be made good physiologically by a minimal increment of work from the remaining fibres; but the loss of a few or even of a single sensory cell in the retina will produce a blind spot in that organ which no amount of activity from the adjoining cells, aside from possible regeneration, can ever replace. Each sensory cell in the more efficient parts of the retina has a function dependent upon its position and, therefore, different from that of any neighboring cell; and, while this may not be absolutely true of all parts of the nervous system, it is vastly more characteristic of nervous structures than of any other organs in the body. While in most systems differentiation may be said to have reached the gross organs, in the nervous system it has extended beyond this to the cellular elements. It follows, therefore, that to know the nervous system anatomically a study of its gross organs is not sufficient; we must know its cellular composition. Hence it is that our more fundamental knowledge of the structure of nervous organs is a product of the present century, the century of cellular research.

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[1] A lecture delivered before the Section of Biology of the New York Academy of Sciences, Jan. 29, 1900.

Although the enunciation of the cell doctrine by Schwann in 1839 was accompanied with a remarkably full description of the cellular components of most animal tissues, including the nervous, it was not until over half a century later that a consistent cellular analysis of nervous organs was accomplished. This was set forth in the conception of the neurone as advanced by the Berlin histologist and anatomist Waldeyer in 1891. The theory of the neurone can best be approached by reviewing briefly the historical steps that lead up to it.

While it is possible that some of the earlier microscopists, and particularly the Scotch anatomist Monro, were acquainted with nerve fibres, the first unquestionable description of these structures was given by Fontana (**1781**), and Stieda, who has reviewed this subject with much care, justly designates this Italian physician as the discoverer of nerve fibres. Fontana's discovery, which for some time failed of the recognition that it deserved, was eventually confirmed by Treviranus (**1816**) and particularly by Ehrenberg (**1833**), whose studies showed that the central nervous organs, as well as the peripheral nerves, were composed of definite fibres. Fontana's work may be regarded as the first step in the modern portrayal of the finer anatomy of nervous organs in that it is the earliest unquestionable description of nerve fibres.

Ehrenberg in the narration of his discoveries not only described and figured nerve fibres, but he also gave an account of other microscopic bodies found in nervous organs, such as crystals, blood corpuscles, and certain roundish bodies which he called "Kugeln" and which subsequent investigators termed ganglion cells. In 1836 Valentine described these ganglion cells with much care, and two years later Remak claimed that in the sympathetic nervous organs of vertebrates ganglion cells were directly connected with nerve fibres. This proposition was supported and broadened by Helmholtz in 1842, who maintained that what Remak had claimed for the vertebrates was also true for invertebrates. Seven years later, in 1849, Kölliker in the first volume of his newly established *Zeitschrift für wissenschaftliche Zoologie* pointed out the inconclusiveness of the observations of Remak and of Helmholtz. The fibres that these authors had described as arising from ganglion cells were marked in no way as indubitable nerve fibres. Doubtless they were nerve fibres, but the histological knowledge of that day, as Kölliker rightly maintained, did not preclude them from being fibres of another kind. Kölliker then proceeded to show that, in the central nervous organs of vertebrates, ganglion cells could be found that were directly connected with fibres possessing medullary sheaths. As medullary sheaths are found only on nerve fibres, it follows that Kölliker's demonstration was the first in which it was shown beyond doubt that nerve fibres are directly connected with ganglion cells. The connection thus demonstrated made it clear that from this time on ganglion cells as well as nerve fibres must be reckoned as essential parts of nervous organs. This may be said to be the second step in the development of our ideas on nervous tectonics.

The third step in this direction was taken by the histologist Leydig, who, in describing the finer anatomy of the arthropods in 1855, stated that the central nervous organs of the spider contained, in addition to ganglion cells and nerve fibres, masses of material composed of many very fine interlacing fibrils. The minutely granular appearance of this material led Leydig to call it "Punktsubstanz," though he did not commit himself to the idea that it was granular rather than finely fibrous. In 1872 Gerlach, by the use of gold chloride, discovered an essentially similar material in the central nervous organs of vertebrates, and, while he assumed for this material a network structure rather than a simple interlacing of fibrils, the facts that he had at hand were in reality much the same as Leydig had previously presented. In both vertebrates and invertebrates it was early recognized that this finely fibrous material was directly continuous with the living substance of both nerve fibres and ganglion cells, and therefore formed an integral part of the nervous organs. To this substance, whether it be from vertebrates or invertebrates, His gave the convenient name of "neuropile."

As no other material aside from the three thus far considered has been found to be necessarily connected with nervous organs, we may regard such organs as made up of a combination of nerve fibres, ganglion, or, as they are often called, nerve cells, and neuropile. The mutual relations of these three materials must next be considered.

The problem of the relation of these nervous materials has been discussed chiefly from the standpoint of the anatomical origin of nerve fibres. When a nerve fibre is traced into a central nervous organ, from what is it found to take its origin? Does it pass out from a ganglion cell, does it originate from the neuropile, or does it come from some other source? This is what is meant by the anatomical origin of nerve fibres, and, on this question the earlier neurologists were divided into three schools. First, there were investigators, like Buchholz, who attempted to maintain that all nerve fibres arose directly from ganglion cells. Next, there were those who, with Leydig at their head, believed that nerve fibres were formed by a drawing together of many fibrils in the neuropile, whereby the transmitting core of a fibre was established. The advocates of this view also believed that the fibrils of the neuropile were derived from the finely divided processes of ganglion cells, and that, therefore, nerve fibres were connected with ganglion cells through the neuropile. Hence they rightly designated their view as that of the indirect origin of nerve fibres as contrasted with the origin of these structures directly from ganglion cells. Finally, there were those who, like Gerlach, maintained that both methods of origin occurred, *i.e.*, that some fibres arose directly from cells and others indirectly through the neuropile. In support of this opinion Gerlach instanced the condition of the spinal nerves in vertebrates (Fig. 1), in which the dorsal fibres spring from the neuropile, *i.e.*, have an indirect origin, and the ventral fibres arise directly from ganglion cells in the ventral horn of the cord. This example was practically conclusive, and later neurologists have been generally free to admit that nerve fibres differ as to their mode of origin, some coming directly from cells, others indirectly, *i.e.*, from the neuropile.

All-absorbing as many of the neurologists of the past found this problem of the anatomical origin of nerve fibres, its solution was followed by no important generalizations. This is probably due to the fact that the views of both the principal contending parties proved to be correct, and the whole conflict, like the inconclusive battles of military history, was lost sight of. But the mass of observations accumulated in the discussion of the anatomical origin of nerve fibres was destined to become a soil from which new growth was to spring. The change that now came over this field of inquiry was in part due to the invention of two new methods of research, Golgi's silver impregnation method and Ehrlich's methylen-blue staining, and in part to a new way of looking at old problems, which, though vastly stimulated by the results obtained through the new methods, was in a measure independent of these. It is note-

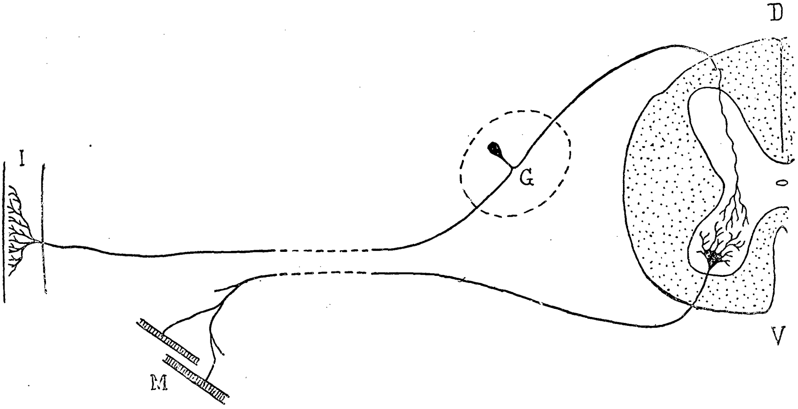

FIG. 1. — Ideal transverse section of vertebrate spinal cord illustrating the extent of a dorsal and of a ventral neurone. The dorsal neurone begins in the integument (*I*), has its cell body situated in the dorsal ganglion (*G*), and enters the cord at the dorsal side (*D*). The ventral neurone has its cell body in the ventral part of the cord (*V*) and is distributed peripherally to muscle fibres (*M*).

worthy that this new departure was initiated to a large extent by one of the oldest working neurologists, Kölliker, who, in his presidential address, delivered before the Anatomische Gesellschaft at Munich, in May, 1891, pointed out the relative unimportance of the problem of the anatomical origin of nerve fibres and raised the really vital question, Is there any nerve fibre not directly connected in some part of its course with a ganglion cell? To this question Kölliker gave a negative reply, and this reply has been confirmed by all subsequent investigators. Every nerve fibre, be it of direct or of indirect origin, is somewhere in its course directly connected with a ganglion cell. In the vast majority of cases the fibres are associated each with a single cell and no more; but in some instances, as, for example, among the worms, fibres are known to be directly connected with several cells.

Kölliker's generalization contains the germ of the neurone theory and leads at once to the statement of that theory as made by Waldeyer in an address before the Berliner medicinische Gesellschaft in June, 1891. This may be stated as follows: The nervous system is not correctly described as composed of nerve fibres, ganglion cells, and neuropile, but it is composed of nervous cells whose bodies we recognize as ganglion cells and whose processes are the cores of the nerve fibres and the neuropile directly connected with these cells. The nervous system then is made up of units, each one of which consists of a ganglion cell provided with longer or shorter processes, the cores of the nerve fibres, and producing from its surface and from that of its fibres fine fibrils, which collectively constitute its neuropile and which bring it into physiological connection with other such units. To these nervous units Waldeyer gave the name "neurones," and the belief that neurones are the structural elements of the nervous system constitutes the neurone theory.

It must be plain from what has been said that each neurone is nothing more than a modified cell. It is characterized, as a rule, by the possession of only one nucleus, and its most obvious peculiarity is that its cytoplasm is in part drawn out into very delicate and enormously elongated processes, the cores of the nerve fibres. If the neurone is only a cell, it should then show the general properties of a cell, and it is from this standpoint that the neurone theory has been most satisfactorily tested. In this connection it is necessary to examine briefly the development of nerves, the degeneration and regeneration of nerves, and the nature of the neuropile.

The development of a nerve was early sketched by Remak (1836) and by Schwann (1839); both maintained that each fibre consisted of a series of cells fused end to end. This view was accepted by many later investigators, notably by the English embryologist Balfour, who showed that in the elasmobranch fishes the nerve fibres were early represented by lines of cells. This hypothesis of the chain structure of nerve fibres was not, however, without its opponents. Von Kupffer seems to have been the first to catch the idea that at least the core or axis cylinder of a nerve fibre was an outgrowth from the ganglion cell. This view was subsequently supported by others, especially by His, whose brilliant investigations on the development of the nerves show beyond a doubt that the axis cylinder is an outgrowth from a ganglion cell (Fig. 2). The forming axis cylinders may become surrounded by cells that eventually develop into the sheath cells of the fibre, and these undoubtedly formed the lines of cells mistaken by many investigators for developing nerve fibres. The resolution of a nerve fibre into a chain of cells, as implied in Remak's original description, is entirely at variance with the neurone theory, but the establishment of the idea that the essential part of every nerve fibre, the axis cylinder, is an outgrowth of a ganglion cell is in perfect accord with it. In the development of its parts, the neurone acts as a single cell; its processes, the axis cylinders of the nerve fibres, are its outgrowths.

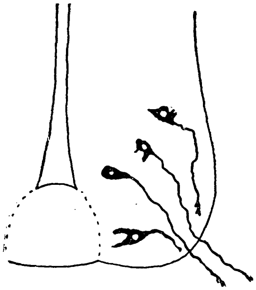

FIG. 2. — Transverse section of the ventro-lateral wall of the developing spinal cord of a chick (in part after Ramon y Cajal). Four cells are shown in process of forming the axis cylinders of future nerve fibres. The outgrowths from the two middle cells have extended beyond the limits of the cord; those of the two other cells still lie within that structure.

The degeneration and regeneration of nerves also afford an opportunity of testing the theory. It has long been known that when a nerve is cut or a bundle of fibres in a central organ injured, some fibres degenerate in one direction, some in another. The question naturally arises, do these degenerations take place in accordance with the assumed cellular nature of the neurone?

Experiments upon large protozoans have shown that when these unicellular animals are cut in two so that one part, which may be the smaller, contains all the nucleus and the other is without even a fragment of this organ, the part without the nucleus invariably soon dies, while that which retained the nucleus may regenerate the lost part and continue to live. The nucleus is in some way absolutely essential to the continued life of the cell.

The same is true of nerve fibres. If a nerve be cut, that portion of each fibre which is thus severed from the nucleus-bearing part, the so-called ganglion cell, invariably dies, even though it remains among the tissues of the body and is bathed in the fluids that are presumed to nourish it. This rule holds for all the degenerations of the nervous organs; after severance the non-nucleated portions of the neurones degenerate precisely as the non-nucleated portion of the protozoan body degenerates. The degeneration of nerve fibres then takes place in accordance with the conception of the neurone as a single cell.

Precisely as the nucleated portion of the divided protozoan body continues to live and may regenerate its lost parts, so the nucleated portion of the neurone remains alive, and, if the injury has not been too severe, may reëstablish itself by throwing out new axis cylinders from the cut end of the old one, and thus new fibres may by growth reëstablish many of the former connections. Regeneration in the neurone, as in the protozoan cell, takes place from the nucleated part; and this phenomenon, as well as that of degeneration, points very clearly to the conclusion that the nucleus of the neurone, like that of any other cell, is a center on which the life of even the most remote portion of the cell is dependent.

This conclusion leads us directly to an important interpretation of the neuropile. If the nucleus of each neurone is a center from which the life of the whole neurone is controlled, then this control must extend, in the case of a given neurone, over that portion of the neuropile associated with it; in other words, the neuropile cannot be considered a diffuse network, as claimed by Gerlach, but must be regarded as divided into provinces, each one of which is under the rule of the neurone with which that particular part is associated (see Fig. 1). The boundaries between these provinces must, then, mark the real limits of the neurones, and that such boundaries actually exist, at least in a physiological sense, is to be inferred from two classes of observations. First, in the degeneration of the central fibres of one of two intimately associated sets of neurones, the degeneration proceeds into the neuropile but not across it, showing that the separation of the neurones lies somewhere in that material. Secondly, since the embryonic cells from which neurones finally develop are in the beginning often widely separated from each other, it follows that their association must be brought about by their gradual growing towards each other, and, as their first step in union would be that of the simple contact of their neuropile masses, it is possible that this relation is all that ever exists and that the points of separation in the neuropile are the original contact points of the developing neurones. For this ingenious suggestion we are indebted to the Swiss neurologist Forel, who, with a keen appreciation of the significance of the embryological investigations made by His, has given us what has been called the Contact Theory of the relation of neurones. This theory, which, when coupled with du Bois-Reymond's hypothesis of a neuropile capable of movement, has been eagerly followed up by many psychologists, is generally supposed to be an essential part of the neurone theory itself; but, though it was undoubtedly so regarded by its earlier advocates, it must be borne in mind that it is in reality not a necessary part of this idea, which has to do with the conception of the neurone unit as a cell rather than with the mutual relations of such units.

The discussion has now led us to a position where a fairly full statement of the grounds for the neurone theory may be made. First, embryology has shown that the nervous system in the beginning is a mass of essentially independent cells, some of which by throwing out processes to form nerve fibres and by other modifications become converted into specially differentiated nervous cells, or neurones. Secondly, the cellular character of each neurone is asserted in later life in that all parts of the neurone remain dependent upon their connection with the nucleus for continued existence and are independent of adjoining neurones. This is seen in the peculiarities of the degeneration and regeneration of nerve, operations that are paralleled in experiments on protozoan cells.

Notwithstanding the obviousness of the cellular nature of the neurone, it must not be forgotten that these cells are of a very exceptional character. Imagine a cell whose nucleated body, scarcely visible to the naked eye, is lodged in the spinal cord of some such animal as an elephant, and whose process, in the form of an axis cylinder as fine as gossamer, stretches from this place through meters of flesh to the animal's foot, and yet the relation of the most distant part of this process to the cell body is so subtile that, should the connection be anywhere severed, the degeneration of the disconnected part invariably follows. It is not strange that such cells as these were not clearly understood by the earlier histologists, for even now they may well excite our wonder.

The objections to the neurone theory are naturally of very recent origin. One of the first to be raised was that of the direct union of cell bodies through their coarser processes. This was found by Dogiel to occur in the ganglionic layers of the retina (Fig. 3), and similar conditions were recorded by other investigators in various nervous organs; but these instances have always proved exceptional, and, while it must be admitted that nervous cells are sometimes united directly, such

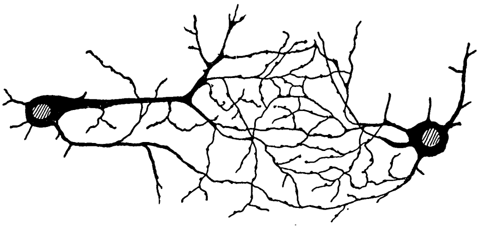

FIG. 3. — Two ganglion cells from the vertebrate retina showing protoplasmic anastomoses (slightly modified from Dogiel).

cases seem to be relatively rare. So far as their bearing on the neurone theory is concerned, I agree with Barker that they form no greater objection to the general theory than the occurrence of Siamese twins does to the general idea that the human species is represented by separate individuals. This form of objection has certainly shown itself to be trivial.

A much more serious obstacle comes from the work associated with the name of Apáthy. This investigator has developed methods which in point of perfection exceed the Golgi and the methylen-blue methods as much as these surpassed the ones before them. Apáthy's methods do not outline neurones; they differentiate the transmitting substance within the neurone. Instead of a coarse nerve fibre or ganglion cell colored homogeneously, one finds a clearly differentiated system of delicate fibrils that constitute collectively the transmitting apparatus of the nervous organs. The peculiarities of Apáthy's methods can be easily appreciated by inspecting the accompanying diagram (Fig. 4), taken from the nervous system

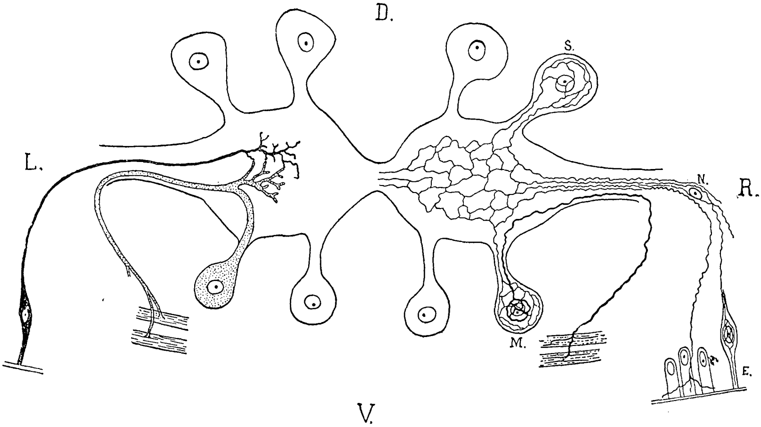

FIG. 4. — Posterior view of a transverse section of the ventral nerve chain of a leech (modified from Apáthy). The median plane of the leech is represented by *D* (dorsal), *V* (ventral). On the left side (*L*), the nervous elements are represented according to the neurone theory, a sensory neurone being represented in solid black, and a motor one dotted. On the right side (*R*) the nervous elements are represented according to Apáthy. The neurofibrils begin in or between the integumentary epithelial cells (*E*), from which they pass centrally into sensory ganglion cells (*S*) or motor ganglion cells (*M*). From the latter, coarse neurofibrils pass peripherally to muscles. The neurofibrils are produced by nerve cells, a nucleus of one of which is shown at *N*.

of the leech and outlined on the left side in accordance with the older methods and on the right after Apáthy. It will be seen at once that Apáthy's methods have to do with the interior of neurones, whereas the older methods dealt with their outlines only. When the fibrillæ so clearly demonstrated by Apáthy are traced, they are found to begin in some cases possibly between the external epithelial cells of the skin, in most cases certainly within these cells, around whose nuclei they form a network, after which they extend as bundles of fine fibrils (sensory nerve fibres) to the central nervous organs. Here they separate, and either enter into the formation of a true network (in what has been called the neuropile) or pass at once into a ganglion cell, in the substance of which they form a network. Ganglion cells of this structure are supposed to be sensory (Fig. 4, *S*). Motor ganglion cells (*M*) are also penetrated by the fibrils from sense organs, which then form a branching system just within the periphery of the cell. From this peripheral system (external plexus) branches extend inward to unite around the nucleus in a second system (internal plexus), from which a single large fibril emerges to make its way eventually as the transmitting organ of a motor fibre to a muscle into whose fibres it may enter after branching. These fibrils are the transmitting organs of the nervous system and are called by Apáthy "neuro-fibrils"; and what is most characteristic about them is that, from their beginnings in or about the sensory cells to their endings in the muscles, they are absolutely continuous; they branch and recombine, but they never show lack of continuity; and this continuity of the fibrillar substance is the feature that characterizes what has been called the fibrillar theory — the supposed opponent of the neurone theory.

Apáthy's opposition to the neurone theory does not stop here, for he has a conception of the structure of the nervous system quite at variance with the tenets of this theory. He holds that the cells connected with nervous operations are of two kinds, which he calls nerve cells and ganglion cells. Nerve cells are those cells that produce fibrillar substance, and this substance in its growth enters sensory cells, ganglion cells, muscle cells, etc.; in short, it is the means of binding the whole nervous system together. Ganglion cells are those cells that produce what is transmitted by the fibrillar substance, namely, nervous impulses.

So far as I am aware, Apáthy has never placed upon record the observations that justify these distinctions, and, as criticism and acceptance of his unsupported statements are equally premature, it seems to me that, till facts are presented, this side of his work must be passed over. If this is done, the character of the fibrillar substance is the only feature of Apáthy's work that requires present consideration. The distribution of this substance is for the most part within neurones. Hence Apáthy's discoveries have to do mostly with the internal anatomy of the neurone, and from this standpoint they afford no ground for attacking the neurone theory. In one respect, however, they bear in an important way on this theory, namely, in the structure they indicate for the neuropile. Is the neuropile a continuous network made up of the anastomoses of neurofibrils, as claimed by Apáthy, or does it lack this continuity in that it is composed of systems of branches derived each from a separate neurone and related only through contact, as implied by the neurone theory?

Apáthy's figures and statements favor in an unqualified way the idea of continuity, but the solution of this problem, one of the most difficult in modern histology, is to be accomplished only by the aid of many hands. It is, therefore, gratifying to find that Bethe has devoted no small amount of time to a critical study of Apáthy's methods and results. Bethe has confirmed many important statements made by Apáthy, but he has been unable to find reasons for accepting Apáthy's distinction of ganglion and nerve cells, and he has shown that Apáthy's generalization of motor fibres, being characterized by one coarse fibril, and sensory fibres by many small ones, does not hold true for the arthropods. He has, however, confirmed the principal statements of Apáthy as to the presence of neurofibrils in nerve fibres and in cells; and, on the important question of the nature of the neuropile, Bethe agrees in his conclusions with Apáthy in stating that it is a continuous network. When, however, the facts for this conclusion are sought for in the body of Bethe's paper, they are found to be not very convincing. In his third study[1] on the central nervous system of the crab (Carcinus), he discusses the question of fibrillar continuity in the neuropile and states that in this animal he has never been able to discover continuity between the fibrils of two neurones, though he has some evidence from the leech that he believes supports this idea and that he proposes to publish later. Such a statement of lack of conclusive evidence on an all-important point can scarcely be called a confirmation of the idea of continuity.

These seem to me the most important contributions made against the neurone theory, and I believe it must be admitted they are not fatal objections. In no case has any one made observations which show that each neurone does not begin as an essentially independent cell, suffering eventually remarkable modifications, but still retaining its character as a single cell. In no case has any one shown that the individuality of the adult neurone, as seen in the degeneration and regeneration of its parts, has suffered any reduction as compared with that of the simple cell from which it came. It seems to me, therefore, that the neurone theory is still intact, and that what has been shown by this new work is that the interior of a neurone has a most delicate and complicated fibrillar structure, which possibly is a means of welding together adult neurones much more closely than has been generally admitted. But of this we have as yet no adequate proof.

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[1] Bethe, Albrecht. Das Centralnervensystem von Carcinus Maenas. Ein anatomisch-physiologisch Versuch. II. Theil. (3. Mittheilung). *Archiv für mikroscop. Anat.* Bd. li, pp. 382–452, Taf. XVI–XVII. 1898.